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EXAMINER	
FALK, ANNE MARIE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/856,230	PRUSINER, STANLEY B.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 July 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-10,18,19,29 and 31-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-10,18,19,29 and 31-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed July 13, 2004 (hereinafter referred to as "the response") has been entered. Claims 1, 9, 10, and 32 have been amended. Claim 2 has been cancelled.

Accordingly, Claims 1, 3-10, 18, 19, 29, and 31-33 remain pending in the instant application.

The terminal disclaimer filed on July 13, 2004 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patent No. 6,020,537 has been reviewed and is accepted. The terminal disclaimer has been recorded.

The double patenting rejection is withdrawn in view of the acceptance of the terminal disclaimer.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-8, 18, 19, 29, and 31 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a prion preparation comprising prions obtained from the brain of a transgenic mouse comprising a genome wherein an exogenous human, bovine, or sheep PrP transgene is operatively inserted and both endogenous PrP alleles are ablated, and wherein the preparation comprises infectious prions (a) which infect and cause disease in an animal chosen from a human, a cow, and a sheep, (b) which are prions of a known strain, (c) the prions are present in a known number of infectious units, and further wherein the carrier is different from brain tissue of the animal chosen from a human, a cow and a sheep, does not reasonably provide enablement for a prion preparation comprising prions obtained from the brain of a transgenic mouse, wherein the transgenic mouse comprises any genetic

modification that renders it susceptible to infection by a human, bovine, or sheep prion. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a standardized prion preparation comprising prions and a carrier, wherein the preparation comprises prions (a) which infect and cause disease in an animal chosen from a human, a cow, and a sheep, (b) which are prions of a known strain, (c) which are present in a known number of infectious units, and further wherein the carrier is different from brain tissue of the animal chosen from a human, a cow, and a sheep.

As amended, the claims broadly cover relatively pure prion preparations, as well as preparations that contain mouse, human, sheep, or cow brain tissue. However, the specification does not disclose relatively pure prion preparations or how to make such preparations, but rather discloses preparations that contain mouse brain tissue.

The specification reveals on pages 25-26 that the DNA sequences of the human, sheep, and cow PrP genes have been determined.

The specification fails to provide an enabling disclosure for the claimed prion preparation because the specification does not teach how to propagate prions from one species of animal, i.e. a human, bovine, or sheep, in a transgenic mouse other than in the brain of the transgenic mouse of the type described in the specification wherein both alleles of the endogenous murine PrP gene are ablated and an exogenous mammalian PrP transgene is operatively inserted. The claims encompass prion preparations isolated from any transgenic mouse having any genetic modification that renders it susceptible to infection by a human, bovine, or sheep prion, but the specification only teaches how to used transgenic mice having a specific type of genetic modification, wherein both alleles of the endogenous murine PrP gene are ablated and an exogenous mammalian PrP transgene is operatively inserted. The specification does not teach how to obtain human, bovine, or sheep prions appropriate for the claimed preparation

(where the carrier is different from brain tissue of the animal chosen from a human, a cow, and a sheep) from anything other than transgenic mice of the type indicated above. Accordingly, the specification does not teach how to propagate human, cow, or sheep prions in any type of transgenic mouse other than a transgenic mouse of the genotype Tg(HuPrP)/Prnp$^{0/0}$, Tg(BovPrP)/Prnp$^{0/0}$, and Tg(ShePrP)/Prnp$^{0/0}$, respectively. The claims encompass human, cow, and sheep prion preparations obtained from the brain of a transgenic mouse, wherein the human, cow, and sheep prions were propagated in the brain of a transgenic mouse having any genetic modification that renders it susceptible to infection with a human, cow, or sheep prion, but the specification does not teach how to accomplish this in anything other than the transgenic mouse of the type indicated above.

Accordingly, the specification fails to provide an enabling disclosure for the preparation of a broad scope of transgenic mice appropriate for the propagation and isolation of exogenous prions because the phenotype of a transgenic mouse cannot be predicted. While the specification discloses transgenic mice wherein both alleles of the endogenous PrP gene have been ablated and an exogenous PrP gene is introduced into the genome, and wherein the mice exhibit an enhanced susceptibility to infection by a prion from a divergent source when compared to non-transgenic mice, the phenotype of any other transgenic mouse harboring a different type of transgene construct cannot be predicted. The specification does not teach what phenotype would be expected in a transgenic mouse, other than a mouse of the type disclosed in the specification. No guidance is provided with respect to how one would have prepared any other type of transgenic mouse exhibiting a transgene-dependent phenotypic alteration which renders it susceptible to infection by a human, cow, or sheep prion. The mere capability to perform gene transfer in a mouse is not enabling for the requisite transgenic mice because the desired phenotype cannot be predictably achieved simply by introducing transgene constructs of interest into the genome of a mouse. While gene transfer techniques are well-developed for a number of species, especially the mouse, methods for achieving the desired level of transgene expression in appropriate tissues are less well-

established. The introduction of DNA into the mammalian genome can ordinarily be achieved most reliably by microinjection or retrovirus-mediated gene transfer. However, the state of the art for transgenics is unpredictable because the method of gene transfer typically relies on random integration of the transgene construct. Insertional inactivation of endogenous genes and position effects (see Wall, 1996, p. 61, paragraph 3) can dramatically influence the phenotype of the resultant transgenic animal. Integration of the transgene near highly active genes or, alternatively, in a transcriptionally inactive region, can influence its level of expression. Furthermore, expression of the transgene and the effect of transgene expression on the phenotype of the transgenic mouse depends on the particular gene construct used, to an unpredictable extent. The particular genetic elements required for appropriate expression are not readily understood. Wall (1996) reports that our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior (p. 61, paragraph 3). With the limited working examples, the production of an appropriate phenotypic alteration (i.e. one that renders the mouse susceptible to infection with a human, cow, or sheep prion) resulting from the introduction of a genetic modification other than that disclosed in the specification (i.e. introduction of an exogenous PrP gene in conjuction with an ablation of both alleles of the endogenous PrP gene), is highly unpredictable.

The specification fails to provide an enabling disclosure for the preparation of the broad scope of transgenic mice covered by the claims because the species barrier, discussed in U.S. Patent No. 5,792,901 (column 14, lines 1-10), makes it difficult to predict whether introduction of a specific PrP transgene (of any species origin) into a host mouse will render the host susceptible to infection with prions obtained from the species that is the source of the exogenously introduced PrP transgene. For example, it is not readily apparent that a mouse harboring a human PrP transgene while also retaining its own endogenous PrP gene would be susceptible to infection with a human prion. Thus, the specification does not teach how to make a transgenic mouse that is susceptible to infection with a human prion in the absence of ablation of both alleles of the endogenous mouse PrP gene.

The specification fails to provide an enabling disclosure for the claimed prion preparations obtained from a transgenic mouse with an exogenous PrP transgene and with a single endogenous PrP allele ablated or with neither allele ablated because the specification teaches that when transgenic mice are made in accordance with the invention, both alleles of the endogenous PrP gene must be ablated in order for the mice to become susceptible to infection with a prion from the species that is the source of the exogenous PrP gene (see, e.g., column 31, Example 8 of U.S. Patent No. 5,792,901). For example, Tg(HuPrP) mice are resistant to infection with human prions.

With regard to Claim 9, the specification fails to provide an enabling disclosure for obtaining prions from Tg(HuPrP), Tg(HuPrP)/Prnp$^{+/0}$, Tg(HuPrP^{CJD}), Tg(HuPrP^{CJD})/Prnp$^{+/0}$, Tg(ShePrP), Tg(ShePrP)/Prnp$^{+/0}$, Tg(BovPrP), Tg(BovPrP)/Prnp$^{+/0}$ mice for the reasons discussed in the preceding paragraph.

The specification fails to provide an enabling disclosure for the claimed prion protein standard for the reasons discussed above regarding the scope of enablement of the transgenic mice that are appropriate for the isolation of exogenous prions.

The specification fails to provide an enabling disclosure for the claimed prion protein standard comprising exogenous prions isolated from any transgenic mouse produced by any genetic manipulation that permits infection by exogenous prions because the specification does not disclose any method for rendering a mouse susceptible to infection by exogenous prions other than by ablating both alleles of the endogenous murine PrP gene and inserting an exogenous PrP gene derived from another species of animal. The claims encompass any genetic manipulation that renders the mouse susceptible to infection by exogenous prions, but the specification is enabling for only one genetic strategy to produce susceptible mice. Furthermore, as discussed above, the phenotype of a transgenic mouse cannot be predicted.

Given the limited guidance in the specification, the limited working examples and the unpredictability in the art, one of ordinary skill in the art would have been required to engage in undue

experimentation in order to make and use appropriate transgenic mice having a genetic modification other than that disclosed in the instant specification. Thus, the skilled artisan would have been required to engage in undue experimentation in order to make the full scope of the claimed prion preparations.

At page 6, paragraph 4 of the response, Applicants argue that they are not claiming a transgenic mouse or a method for producing a transgenic mouse. However, the claims cover compositions isolated from transgenic mice. As such, the claims must be enabled to their full scope. Since relatively pure prion preparations are not disclosed, the prion preparations will vary depending on the source material. Prion preparations isolated from human brain tissue will contain contaminating material from human brain tissue, whereas prion preparations isolated from mouse brain tissue will not contain human brain tissue material, but will contain contaminating material from mouse brain tissue. It is the role of the specification to enable the full scope of the claimed compositions. Since the compositions will vary depending on the source material and mode of preparation, it is the role of the specification to enable appropriate source material. Since the claimed compositions could be isolated from a transgenic mouse that has any genetic modification that renders them susceptible to infection with human, cow, or sheep prions, it is the role of the specification to enable the full scope of source material, i.e. the transgenic mice. However, the specification only discloses a particular type of genetic modification that renders mice susceptible to infectious human, cow, or sheep prions, namely those that comprise a genome having both endogenous PrP alleles ablated and an exogenous human, bovine, or sheep PrP transgene operatively inserted. Thus, the specification has enabled only one type of source material beyond that known in the prior art (as discussed below) and the composition of the claimed prion preparations will depend on the composition of that source material.

Thus, the rejection is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 29 and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 32 is indefinite in its recitation of conflicting broad and narrow limitations within the same claim. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, Claim 32 recites the broad recitation "a human, a cow, and a sheep", and the claim also recites Tg(BovPrP)Prnp$^{0/0}$ which is the narrower statement of the range/limitation. A bovine prion would not be expected to infect and cause disease in a human and a sheep.

Claim 29 is indefinite in its recitation of "the transgenic mouse brains" because the phrase lacks antecedent basis. Claim 1 does not recited "transgenic mouse brains."

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4, and 6 are rejected under 35 U.S.C. 103(a) as being unpantentable over Stahl et al. (1991, FASEB Journal 5: 2799-2807).

The claims are directed to a standardized prion preparation comprising prions and a carrier, wherein the preparation comprises prions (a) which infect and cause disease in an animal chosen from a human, a cow, and a sheep, (b) which are prions of a known strain, (c) which are present in a known number of infectious units, (d) which are present in a known concentration and further wherein the carrier is different from brain tissue of the animal chosen from a human, a cow, and a sheep.

Stahl et al. (1991) disclose that extracts of brain tissue from GSS and CJD afflicted individuals can transmit a scrapie-like disease to experimental animals (page 2799, column 1, paragraph 2). The brain extracts constitue prion preparations that comprise infectious prions. The solvent used in the extraction would constitute the carrier. As recited in the claims, the carrier is not animal brain tissue; it is the solvent that is combined with the tissue to produce the extract. The prions are of a known strain because they are obtained from individuals afflicted with either GSS or CJD. One of skill in the art would readily recognize that prions obtained from a patient with CJD would be CJD-strain prions even if details of the molecular structure of the CJD prion protein of the particular patient were not known. The reference discloses several human variants in the legend to Figure 1. At page 2801, column 1, paragraph 3, the reference discloses that a pathogenic point mutation that changes Pro-102 to Leu was found in families with ataxic GSS, with the occurrence of the disease tightly linked to this mutation. The reference further discloses that ELISA assays have been used to determine the concentration of infectious prions in hamster brain tissue (page 2800, column 1, paragraph 2).

Since one of skill in the art would have been interested in detecting and quantitating infectious prions in various types of samples, particularly human tissue samples, the skilled artisan would have been

motivated to make a prion preparation of a known concentration for the purpose of using said prion preparation in comparing different prion protein detection assay methods to determine which assay methods were the most reliable or to develop improved assay methods that are either more precise or more accurate or both. One skilled in the art would have anticipated a reasonable expectation of success because appropriate infectious prion preparations as disclosed by Stahl et al. were available and only standard scientific methodology is required to measure prion concentrations and determine the number of infectious units. The reference itself discloses the ELISA assay as one example of a methodology for determining prion concentration.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

At page 6, paragraph 5 of the response, Applicants argue that "one skilled in the art could isolate prions from a diseased brain of a human, cow or sheep, mix those prions into a carrier, test the resulting preparation to determine that is does cause infection, determine its strain and determine the number of infectious units as well as the concentration of prions in the preparation." Thus, it is evident that Applicants contend that such a preparation, isolated from a diseased brain of a human, cow or sheep, would meet the claim limitations. Although the claims recite the limitation "wherein the carrier is different from brain tissue of the animal chosen from a human, a cow and a sheep" it does not require that the **preparation** as claimed be free of human/cow/sheep brain tissue. Thus, the claims are construed to cover prion preparations isolated from human brain tissue, bovine brain tissue, and sheep brain tissue when combined with a carrier, such as phosphate buffered saline, for example.

Conclusion

Claims 9, 10, and 33 are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on (571) 272-0804. The central official fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER